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Asymmetric hydrogenation of 2-substituted *N*-protected-indoles catalyzed by rhodium complexes of BINOL-derived phosphoramidites

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ABSTRACT

The rhodium-catalyzed asymmetric hydrogenation of 2-substituted *N*-protected-indoles using monodentate phosphoramidites as ligands was examined. Full conversion and 74% ee, were obtained with a catalyst based on PipPhos. The use of a catalytic amount of base is necessary for activity; best results were obtained with Cs₂CO₃.

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1. Introduction

One of the approaches for the preparation of enantiopure saturated heterocycles is via asymmetric hydrogenation of heteroaromatic compounds. Despite considerable progress in this field, hydrogenation of aromatic and heteroaromatic compounds with high enantioselectivity still remains a great challenge.¹

Enantiopure indoline-2-carboxylic acid is an important intermediate for angiotensin I converting enzyme inhibitors (ACE inhibitors) which have found application in the treatment of hypertension such as perindopril,² pentopril, and indolapril (Fig. 1).³ The preparation of enantiopure (*S*)-indoline-2-carboxylic acid and its methyl ester is generally achieved via classical resolution,⁴ chemical synthesis through asymmetric reduction with a chiral auxiliary⁵ or via enzymatic methods such as resolution via hydrolysis of indole-2-carboxylic esters,^{6a–d} or using phenylammonia lyase for the preparation of *ortho*-chlorophenylalanine followed by a copper-catalyzed ring closure.^{6e} Fu et al. have reported a kinetic resolution of 2-substituted indoles via acylation using a chiral base as a catalyst.⁷

In the resolution methods, the yield never exceeds 50%. The synthesis method through asymmetric reduction using a chiral auxiliary involves the NaBH₄ reduction of prochiral 3-(*ortho*-nitro-phenyl)pyruvic acid applying the chiral auxiliary *D*-proline. The resulting alcohol derivative is then converted into enantioenriched (*S*)-indoline-2-carboxylic acid via four synthetic steps with an overall yield of 32%, using expensive *D*-proline.⁵

In 2000, Ito et al. reported the asymmetric hydrogenation of 2-substituted *N*-acetyl and *N*-Boc-protected indoles with excellent conversions and enantioselectivities (up to 95% and 78% ee, respectively) using a rhodium catalyst with the *trans*-chelating bis-phos-

phine ligand Ph-TRAP and Cs₂CO₃ as a base.⁸ They found that the base has an important role in obtaining both good catalytic activity and enantioselectivity. Later, Kuwano et al. reported the Rh-catalyzed asymmetric hydrogenation of *N*-tosyl-3-substituted indoles⁹ and the Ru-catalyzed hydrogenation of *N*-protected-2- and 3-substituted indoles with excellent enantioselectivities and conversions using the same Ph-TRAP ligand.¹⁰

We have developed the use of phosphoramidite ligands in rhodium-, ruthenium-, and iridium-catalyzed asymmetric hydrogenation of olefins, ketones, and imines.¹¹ We have also recently reported the asymmetric hydrogenation of 2,6-substituted quinolines¹² using an iridium catalyst with the monodentate phosphoramidite ligand (*S*)-PipPhos **1a**, with excellent conversions and ee's. Phosphoramidites have the advantage of being readily accessible, highly diverse, air stable, and inexpensive compared to most bidentate ligands.¹³ In addition, they are amenable to parallel synthesis.¹⁴ Herein, we report the asymmetric hydrogenation of 2-substituted *N*-protected indoles using rhodium-based catalysts with monodentate phosphoramidite ligands.

2. Results and discussion

The initial screening of reaction conditions was performed in dichloromethane at various hydrogen pressures and temperatures using methyl *N*-acetylindole-2-carboxylate **1a** as a substrate, 5 mol % of [Rh(COD)₂]BF₄ precursor, and 10 mol % of monodentate (*S*)-PipPhos (Table 1). In reactions without additives (entries 1 and 2) no conversion was detected at room temperature and only low conversion and enantioselectivity were observed at 40 °C. As reported by Ito, the addition of a base seems to be crucial in these hydrogenations.⁸ Indeed, when 10 mol % of cesium carbonate was added to the hydrogenation of **1a**, full conversion and ee's up to 74% were obtained (entries 3–7). Further experiments established that 40 °C is optimal, pressure has no influence and other bases gave much poorer results. The addition of tri-*o*-tolylphosphine as

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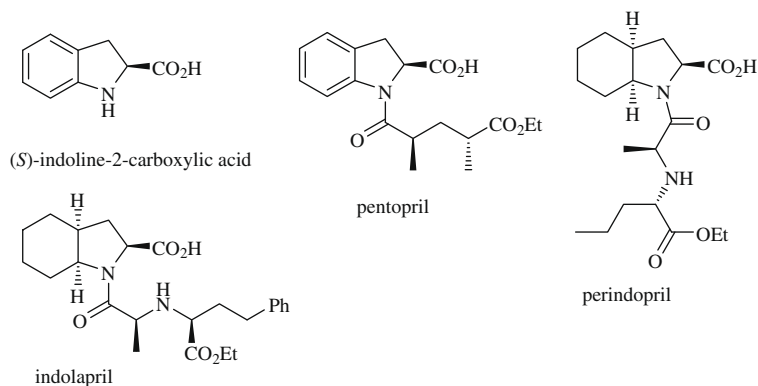
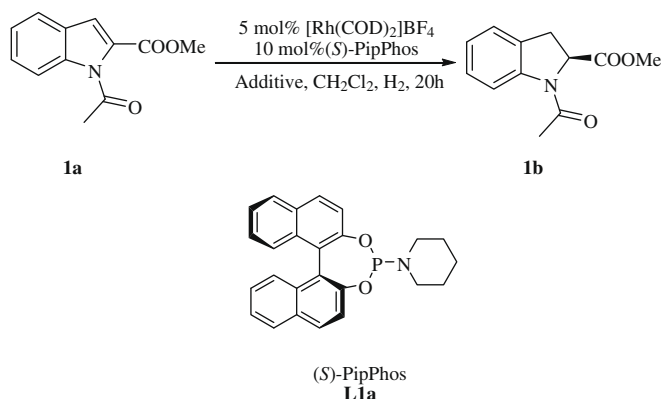


Figure 1. (S)-Indoline-2-carboxylic acid and the ACE inhibitors indolapril, pentopril and perindopril.

Table 1
Asymmetric hydrogenation of **1a** using $[\text{Rh}(\text{COD})_2]\text{BF}_4/(\text{S})\text{-PipPhos}$ as a pre-catalyst^a



Entry	Additive	Temp (°C)	Conv. ^b (%)	ee ^c (%)
1	—	25	0	—
2	—	40	13	12
3	10% Cs ₂ CO ₃	25	100	73
4 ^d	10% Cs ₂ CO ₃	25	100	68
5	10% Cs ₂ CO ₃	40	100	74
6	20% Cs ₂ CO ₃	40	95	38
7	10% Cs ₂ CO ₃	60	71	61
8	10% CsF	40	100	72
9	10% KOAc	40	66	60
10	10% Na ₂ CO ₃	40	2	—
11	10% Li ₂ CO ₃	40	16	20
12	10% KH ₂ PO ₄	40	15	10 ^e
13	10% Et ₃ N	40	100	55
14 ^f	10% Cs ₂ CO ₃	25	65	49

^a Reaction conditions: 0.2 mmol of **1a**, 0.01 mmol of $[\text{Rh}(\text{COD})_2]\text{BF}_4$, 0.02 mmol of (S)-PipPhos, 0.02 mmol of Cs₂CO₃, 25 bar of H₂, and 4 mL of CH₂Cl₂.

^b Conversion was determined by ¹H NMR.

^c Enantioselectivity was determined by GC.

^d 100 bar H₂.

^e The opposite configuration of the product was obtained.

^f Extra added PPh₃ (Rh/PipPhos/PPh₃ = 1:2:1)

an achiral ligand (mixed ligand approach,^{15,16} Rh/L*/L = 1/2/1) did not lead to further improvement (65% conversion, 49% ee, entry 14).

We also examined the influence of the solvent on the reaction outcome using cesium carbonate as an additive (Table 2). The best result was obtained in dichloromethane (entry 1). The use of other solvents led to much reduced rate and enantioselectivities.

Various phosphoramidite ligands **L1a–i**, **L2** were tested under the optimal reaction conditions in the asymmetric hydrogenation of **1a** (Table 3). The best result was still obtained with (S)-PipPhos **L1a** (entry 1). Excellent conversion and an ee of 59% were achieved

Table 2
Solvent screening in the asymmetric hydrogenation of **1a**^a

1a $\xrightarrow[10 \text{ mol}\% (\text{S})\text{-PipPhos}]{5 \text{ mol}\% [\text{Rh}(\text{COD})_2]\text{BF}_4, 10 \text{ mol}\% \text{Cs}_2\text{CO}_3, \text{Solvent}, 40^\circ\text{C}, 25 \text{ bar H}_2}$ **1b**

Entry	Solvent	Conv. ^b (%)	ee ^c (%)
1	CH ₂ Cl ₂	100	74
2	EtOAc	59	27
3	<i>i</i> -PrOH	95	8
4	MeOH	0	—
5	THF	16	4
6	Toluene	62	5

^a Reaction conditions: 0.2 mmol of **1a**, 0.01 mmol of $[\text{Rh}(\text{COD})_2]\text{BF}_4$, 0.02 mmol of (S)-PipPhos, 0.02 mmol of Cs₂CO₃, 4 mL of solvent, 40 °C, and 25 bar of H₂.

^b Conversion was determined by ¹H NMR.

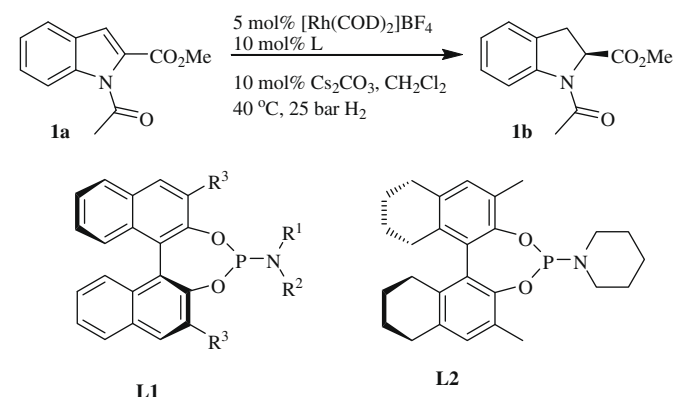
^c Enantioselectivity was determined by GC.

with the ligand derived from azepane (**L1e**, entry 5), while pyrrolidine-derived ligand **L1d** induced a very low ee (Entry 4). With MonoPhos **L1b**, 77% conversion and 33% ee were obtained, whereas the use of ligand **L1c** surprisingly gave no conversion (entries 2 and 3).

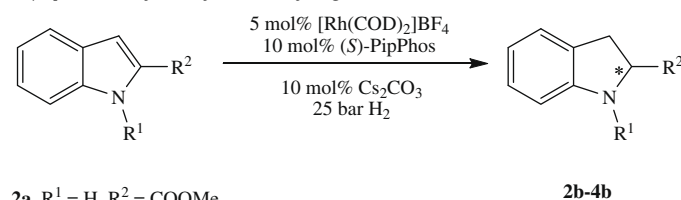
Some other indole derivatives were also screened using (S)-PipPhos at 25 bar of hydrogen pressure (Table 4). The hydrogenation of unprotected ester **2a** to indoline **2b** did not proceed, at room temperature or 40 °C, with or without the addition of a base (entry 1, other conditions not shown). This seems to imply that the protective group on the nitrogen is required in order to achieve coordination of the substrate to the metal. Boc-protected substrate **3a** was hydrogenated with 48% conversion, surprisingly only 4% ee was found (entry 2). Hydrogenation of acid **4a**, was achieved with low ee, (entries 3 – 6). The best result was obtained in dichloromethane, with the addition of cesium carbonate (54% conversion, 37% ee, entry 4).

3. Mechanistic considerations

No mechanistic proposals have been published for the base dependent rhodium-catalyzed asymmetric hydrogenation of indoles. In view of the fact that a catalytic amount of base suffices, the assumption seems justified that the base is part of the catalytic cycle. This is a well-known phenomenon in ruthenium-catalyzed hydrogenations, where the base serves to create a ruthenium monohydride species, which is the actual catalyst.¹⁷ Thus, we pro-

Table 3Ligand screening for the asymmetric hydrogenation of **1a**^a

Entry	Ligand	Conv. ^b (%)	ee ^c (%)
1	(S)- L1a R ¹ , R ² = -(CH ₂) ₅ -, R ³ = H	100	74
2	(S)- L1b R ¹ , R ² = Me, R ³ = H	77	33
3	(S)- L1c R ¹ , R ² = <i>i</i> -Pr, R ³ = H	0	—
4	(S)- L1d R ¹ , R ² = -(CH ₂) ₄ -, R ³ = H	64	2
5	(S)- L1e R ¹ , R ² = -(CH ₂) ₆ -, R ³ = H	93	59
6	(S)- L1f R ¹ , R ² = <i>o</i> -CH ₂ C ₆ H ₄ CH ₂ CH ₂ -, R ³ = H	87	10
7	(R)- L1g R ¹ , R ² = (S)-PhCH(CH ₃) ₃ -, R ³ = H	9	26 ^d
8	(S)- L1h R ¹ , R ² = (S)-PhCH(CH ₃) ₃ -, R ³ = H	0	—
9	(R)- L1i R ¹ , R ² = -(CH ₂) ₅ -, R ³ = Me	60	24 ^e
10	(R)- L2	64	31 ^e

^a Reaction conditions: see Table 1 with the exception of *T* = 40 °C.^b Conversion was determined by ¹H NMR.^c Enantioselectivity was determined by GC.^d Absolute configuration was determined by comparison of the sign of the specific rotation with literature data.^e Opposite configuration of the product observed.**Table 4**Rh/PipPhos-catalyzed asymmetric hydrogenation of indoles^a**2a**, R¹ = H, R² = COOMe**3a**, R¹ = Boc, R² = COOMe**4a**, R¹ = Acetyl, R² = COOH

Entry	Indoline	Solvent	Cs ₂ CO ₃	<i>T</i> (°C)	Conv. ^b (%)	ee ^c (%)
1	2b	CH ₂ Cl ₂	+	25	0	—
2	3b	CH ₂ Cl ₂	+	40	48	4
3	4b	CH ₂ Cl ₂	—	40	5	22
4	4b	CH ₂ Cl ₂	+	40	54	37
5	4b	Toluene	+	40	50	23
6	4b	HOAc	—	40	4	13

^a Reaction conditions: 0.2 mmol of substrate, 0.01 mmol of [Rh(COD)₂]BF₄, 0.02 mmol of PipPhos, 0.02 mmol of Cs₂CO₃, 4 mL of solvent, 40 °C, and 25 bar of H₂.^b Conversions were determined by ¹H NMR.^c Enantioselectivities were determined by HPLC.

pose the mechanism as pictured in Scheme 1. After the formation of the cationic bisligated rhodium COD-complex **A**, the reaction with hydrogen furnishes dihydrogen complex **B**, which upon reaction with base forms the neutral rhodium monohydride complex **C**. The reaction with the substrate gives complex **D**. Insertion of the indole olefin into the rhodium hydride bond leads to the formation of rhodiumalkyl complex **E**, which reacts with dihydrogen to yield the product and reform hydride **C**. Trzeciak and co-workers have shown that isolated rhodium monohydride complexes are good catalysts for the hydrogenation of aromatic compounds.¹⁸ To date, we have not been able to observe any intermediates using ES-MS.

4. Conclusion

In conclusion, full conversion and up to 74% ee have been obtained in the asymmetric hydrogenation of methyl *N*-acetyl-indole-2-carboxylate **1a** using 5 mol % of rhodium catalyst with 10 mol % of monodentate phosphoramidite ligand PipPhos and 10 mol % of cesium carbonate. A protecting group on the nitrogen was shown to be crucial for obtaining conversion. The presence of cesium salts has been shown to be necessary to obtain a high ee. The Boc-protected indole ester **3a** was hydrogenated with 48% conversion and only 4% ee, while *N*-acetyl-indole-2-carboxylic acid **4a** was hydrogenated with up to 54% conversion and 37% ee.

5. Experimental section

5.1. General remarks

The catalysts were prepared in situ. Hydrogenation reactions were performed in a stainless steel autoclave containing seven glass vessels (8 mL volume). Magnetic stir bars were placed inside each vessel, the vessels were closed with septum caps, and the septa were pierced with syringe needles in order to enable the entrance of hydrogen. The autoclave was filled under air and then flushed with nitrogen before hydrogen pressure was applied. NMR spectra were obtained on Varian AMX400 and VXR500 spectrometers. Chemical shifts are given in parts per million (ppm) relative to the residual solvent peak. GC analysis was carried out on an HP6890 using a flame ionization detector, while HPLC analysis was performed on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. The enantiomeric excess was determined by HPLC with chiral columns (Chiralcel OD and OD-H) or by GC with Chirasil DEX CB, in comparison with racemic products. Optical rotations were measured on a Schmidt and Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL).

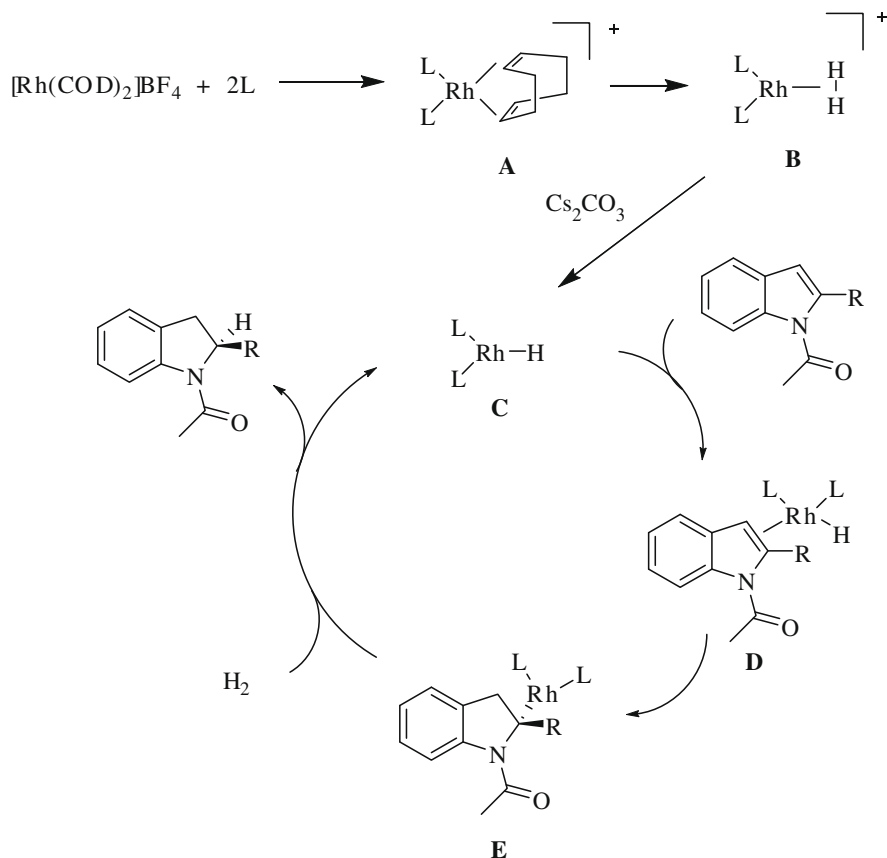
Ligands **L1a**,¹⁹ **L1b**,¹⁹ **L1c**,¹⁹ **L1d**,²⁰ **L1e**,²⁰ **L1f**,²⁰ **L1g**,¹⁹ **L1h**,¹⁹ **L1i**,²¹ and **L2**²¹ were prepared according to the literature procedures. Substrates **1a**, **2a**, and **3a** were prepared according to the literature.⁸ Substrate **4a** was obtained as a gift from DSM Pharmaceutical Chemicals, Venlo, The Netherlands. Products **1b** and **3b** are known compounds.⁸

5.2. General procedure for hydrogenation

A mixture of [Rh(COD)₂]BF₄ (4.06 mg, 0.01 mmol), (S)-PipPhos (7.99 mg, 0.02 mmol), substrate (0.2 mmol), and a base (0.02 mmol) were dissolved in 4 mL of solvent, in a glass vial equipped with a stirrer bar. The vial was placed in a stainless steel autoclave. After the reaction, hydrogen pressure was carefully released. The solvent was removed in vacuo and conversion was determined by ¹H NMR. The product was purified on silica.

5.3. 1-Acetyl-2,3-indoline-2-carboxylic acid **4b**

This compound exists as mixture of two configurations due to the hindered rotation of the acetyl moiety. Both configurations are observed at rt by ¹H and ¹³C NMR. At 60 °C, only one configuration was observed (broad signals). White solid; ¹H NMR (500 MHz, (CD₃)₂NCOD, 60 °C) 2.38 (s, 3H), 3.46–3.48 (br, 1H), 3.82–3.84 (br, 1H), 5.37 (d, *J* = 8.63 Hz, 1H), 7.20 (t, *J* = 7.35 Hz, 1H), 7.38–7.44 (m, 2H), 8.36 (br, 1H), 13.3 (br, 1H) ppm; ¹³C NMR (125 MHz, (CD₃)₂NCOD, 60 °C) 23.3, 33.5, 61.5, 116.6, 123.5, 124.8, 127.5, 129.9, 143.6, 169.2, 173.4 ppm; HPLC (OD, eluent: heptane/*i*-PrOH/HCOOH = 80/20/1, detector: 254 nm, flow rate: 1 mL/min), *t*₁ = 9.7 min, *t*₂ = 11.2 min.



Scheme 1. Proposed hydrogenation mechanism.

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